pound intramusculary. After the assay, all monkeys were given standard malarial treatment. Specifically, seven-day primaquine (1.78 mg/kg) and chloroquine (10 mg/kg) were administered to treat all monkeys. The results are shown in Table 6:

TABLE 6

Causal Prophylactic Activity of 5e, 6c, 7a and 7c in *P. cynomolgi* Sporozoites Challenged Rhesus Monkeys@

Compd #	Dose (mg/kg)	**Days Treated	Route	Results	Patency (Days Post-innoculation)
Control	N/A*	1 daily for 3 days	IM	Valid Control	8 days 8 days
5e	30	1 daily for 3 days	IM	Delayed +Patency for 19 to 21 days	27 days 29 days
6c	30	1 daily for 3 days	IM	Delayed Patency for 54 days Delayed Patency for 86 days	62 days 94 days
7a	30	1 daily for 3 days	IM	Delayed Patency for 5 to 9 days	13 days 17 days
7c	30	1 daily for 3 days	IM	Delayed Patency for 13 to 32 days	21 days 40 days

@Two monkeys per dose group.

*At the same volume as other experimental groups. Maximum DMSO volume per site is 1 mL of 2 injection sites (one in each thigh).

**Drugs were dissolved in DMSO and given on days before, on the day and a day after (−1, 0, +1 day) sporozoites inoculation.

+First day the parasite can be detected in blood smears after infection.

The results indicated that all compounds tested displayed protection in monkeys. Carboxamide derivative 7a showed weak causal prophylactic activity in Rhesus test, prolonged the patency for 5 days to one monkey and 9 days for the other. Carboxamide 7c, however, showed superior protective activity than that of 7a, delayed patency 13 days for one of the treated monkeys and 32 days for the other. Benzyloxy derivative 5e was about equal in causal prophylactic activity to 7c, delayed patency for treated monkey from 19 to 21 days at doses of 30 mg/kg/day for 3 days by IM. Among the 4 compounds tested, 6c exhibited the most potent causal prophylactic activity, delayed patency for 54 days in one treated monkey and the other for 86 days.

The monkeys were only treated for 3 days in the experiments, instead of 7 days for 8-aminoquinoline antimalarials, such as primaquine and tafenoquine, in the reported protocols (E. Beutler, *Blood,* 14 (2), 103-139 (1959); P. Phillips-Howard et al., *Drug Safety* 12:370-383 (1995); P. Schlagenhauf, *J Travel Med* 6:122-123 (1999)). Thus, longer treatment with the test compounds can lead to higher rate of cures. In addition, no adverse side effects was observed in the monkeys treated with the test compounds at the level of 30 mg/kg×3 days, indicating that longer treatments would be tolerated.

b. Radical Cure Test in Rhesus Monkeys:

Assessment of radical curative activity of the test compounds was carried out using the monkeys that developed parasitemia during the causal prophylactic experiments when the test compounds showed no or weak activity. Monkeys were treated with chloroquine (10 mg/kg/day) by oral for 7 consecutive days and the test compounds by IM for 3 consecutive days after the parasitemia level reached 5,000 parasites/mm^3. Chloroquine (CQ) at 10 mg/kg/day×7 days eliminates the blood stage parasites, but not the liver stage hypnozoites. Compounds with antihypnozoite activity will delay the relapse or radically cure the infection. To evaluate the radical curative properties, daily blood samples were followed for 21 days, 3 times per week for 4 weeks, and then 2 times weekly until 100 days after the last day of test compound administration. Parasite clearance should occur in all animals treated with chloroquine. Relapse is expected in the control group. Relapse in the treated group indicates failure of the test compounds. Monkeys showed no relapse after 100 days are considered radically cured. Relapses of the control monkeys were treated with chloroquine once daily for 7-days and observed for a second relapse. Relapse in experimental animals and the second relapse of the control monkeys were treated with the standard 7-day oral CQ (chloroquine) and primaquine (1.78 mg base/kg). After standard treatment, blood smears were monitored daily for 4 consecutive days of negative results and 2 times weekly for 2 weeks. The results are shown in Table 7.

TABLE 7

Radical Curative Activity of Compounds in 5e, 5c, 7a and 7c Relapsed Rhesus Monkeys.

Group No.	Drug 1	Drug 2	Dose (mg/kg)	# Doses per Day	Route	Results	Days Post-treatment
1	CQ, 10 mg/kgx7, po		None		Oral	Relapse	9 days 9 days
2	CQ, 10 mg/kgx7, po	5e	30	1 daily for 3 days	IM	Delayed relapse	35 days 33 days
3		6c	30	1 daily for 3 days	IM	Delayed relapse	66 days 91 days
4		7a	30	1 daily for 3 days	IM	Delayed relapse Cure	16 days Radical cure
5		7c	40	1 daily for 3 days	IM	Delayed relapse	29 days 32 days

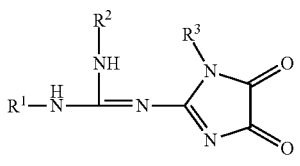
All of the compounds tested delayed relapse compared to the control group. One out of two monkeys treated with 7a was cured. The other treated monkey showed delayed relapse for 16 days, 7 days longer as compared with untreated control animals. Compound 7c delayed relapse in one monkey for 29 and the other for 32 days, 20 and 23 days longer, respectively, as compared with control animals. Compound 6c was more active than 5e, 7a and 7c in radical curative efficacy test.

Having thus described exemplary embodiments of the present invention, it should be noted by those skilled in the art that the written disclosures are exemplary only and that various other alternatives, adaptations, and modifications can be made within the scope of the present invention.

What is claimed is:

1. A compound having the formula I:

(I)



or a tautomer thereof, or their pharmaceutically acceptable salts,